


REMARKS

Claims 1-135 have been canceled without prejudice. New claims 136-204 have been added. Support for the new claims is found throughout the specification and claims as originally filed. No new matter has been added by way of these amendments. A copy of the claims pending in the instant application is attached hereto as Exhibit A.

Respectfully submitted,

Date: September 30, 2002

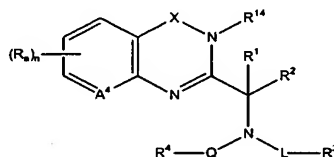

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Enclosures

EXHIBIT A
CLAIMS PENDING IN THE INSTANT APPLICATION
U.S. PATENT APPLICATION SERIAL NO. 10/015,532

136. A compound having the formula:



or a pharmaceutically acceptable salt or prodrug thereof wherein:

A⁴ is N;

X is -C(O)-, -CH₂- or a bond;

R¹ and R² are members independently selected from the group consisting of H and (C₁-C₄)alkyl;

R³ is a member selected from the group consisting of hydroxy, (C₁-C₈)alkoxy, amino, (C₁-C₈)alkylamino, di(C₁-C₈)alkylamino, (C₂-C₈)heteroalkyl, (C₃-C₉)heterocyclyl, (C₁-C₈)acylamino, amidino, guanidino, ureido, cyano, heteroaryl, -CONR⁹R¹⁰ and -CO₂R¹¹;

R⁴ is a member selected from the group consisting of (C₁-C₂₀)alkyl, (C₂-C₂₀)heteroalkyl, heteroaryl, aryl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₆)heteroalkyl, aryl(C₁-C₆)alkyl and aryl(C₂-C₆)heteroalkyl;

each R⁹, R¹⁰ and R¹¹ is independently selected from the group consisting of H, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, heteroaryl, aryl, heteroaryl(C₁-C₆)alkyl, heteroaryl(C₂-C₈)heteroalkyl, aryl(C₁-C₈)alkyl and aryl(C₂-C₈)heteroalkyl;

R¹⁴ is substituted or unsubstituted aryl or heteroaryl;

Q is -C(O)-;

L is (C₁-C₈)alkylene;

the subscript n is an integer from 0 to 4; and

each R_n is independently selected from the group consisting of halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂,

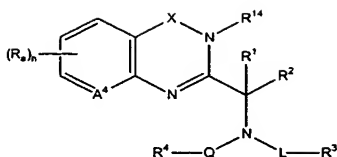
perfluoro(C₁-C₄)alkoxy and perfluoro(C₁-C₄)alkyl, wherein R', R" and R''' are each independently selected from the group consisting of H, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, unsubstituted aryl, unsubstituted heteroaryl, (unsubstituted aryl)-(C₁-C₄)alkyl and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

137. The compound of Claim 136, wherein X is -C(O)-.
138. The compound of Claim 136, wherein R¹⁴ is a substituted or unsubstituted member selected from the group consisting of phenyl, pyridyl, thiazolyl, thienyl and pyrimidinyl.
139. The compound of Claim 137, wherein R¹⁴ is a substituted or unsubstituted member selected from the group consisting of phenyl, pyridyl, thiazolyl, thienyl and pyrimidinyl.
140. The compound of Claim 136, wherein R³ is (C₁-C₈)acylamino.
141. The compound of Claim 136, wherein R⁴ is substituted or unsubstituted benzyl, wherein said substituents are selected from the group consisting of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyano, nitro and phenyl.
142. The compound of Claim 136, wherein R¹⁴ is selected from the group consisting of substituted phenyl, substituted pyridyl, substituted thiazolyl and substituted thienyl, wherein the substituents are selected from the group consisting of cyano, halogen, (C₁-C₈)alkoxy, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, CONH₂, methylenedioxy and ethylenedioxy.
143. The compound of Claim 136, wherein R¹⁴ is substituted phenyl, wherein the substituents are selected from the group consisting of cyano, halogen, (C₁-C₈)alkoxy, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, CONH₂, methylenedioxy and ethylenedioxy.
144. The compound of Claim 136, wherein R⁴ is substituted or unsubstituted benzyl, wherein said substituents are selected from the group consisting of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyano, nitro and phenyl, and R¹⁴ is substituted phenyl, wherein the substituents are selected from the group consisting of cyano, halogen, (C₁-C₈)alkoxy, (C₁-C₈)alkyl, (C₂-C₈)heteroalkyl, CONH₂, methylenedioxy and ethylenedioxy.
145. The compound of Claim 136, wherein R¹ is selected from the group consisting of methyl, ethyl and propyl, and R² is hydrogen.
146. The compound of Claim 136, wherein R¹ and R² are each methyl.
147. The compound of Claim 136, wherein L is (C₁-C₄)alkylene.

148. The compound of Claim 136, wherein R³ is a member selected from the group consisting of (C₁-C₈)alkoxy, (C₃-C₉)heterocyclyl and heteroaryl.
149. The compound of Claim 136, wherein R³ is heteroaryl.
150. The compound of Claim 136, wherein R³ is heteroaryl and R⁴ is substituted or unsubstituted benzyl, wherein said substituents are selected from the group consisting of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyano, nitro and phenyl.
151. The compound of Claim 136, wherein R³ is selected from the group consisting of substituted or unsubstituted pyridyl and substituted or unsubstituted imidazolyl.
152. The compound of Claim 136, wherein R¹ and R² are each independently selected from the group consisting of H, methyl and ethyl; R¹⁴ is phenyl; L is methylene, ethylene or propylene; R³ is selected from the group consisting of substituted or unsubstituted pyridyl and substituted or unsubstituted imidazolyl; and R⁴ is substituted or unsubstituted benzyl, wherein said substituents are selected from the group consisting of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyano, nitro and phenyl.
153. A pharmaceutical composition comprising the compound of Claim 136 and a pharmaceutically acceptable carrier or diluent.
154. A method of treating an inflammatory or immune condition or disease in a subject, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of Claim 136.
155. The method of Claim 154, wherein said compound is administered orally, parenterally or topically.
156. The method of Claim 154, wherein said compound modulates CXCR3.
157. The method of Claim 154, wherein said compound is a CXCR3 antagonist.
158. The method of Claim 154, wherein said inflammatory or immune condition or disease is selected from the group consisting of neurodegenerative diseases, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, atherosclerosis, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, psoriasis, eczema, urticaria, type I diabetes, asthma, conjunctivitis, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, Behcet's syndrome, gout, viral infections, bacterial infections, organ transplant conditions and skin transplant conditions.
159. The method of Claim 158 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.
160. The method of Claim 154, wherein said compound is administered in combination with a second therapeutic agent, wherein said second therapeutic agent is useful for

treating neurodegenerative diseases, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, atherosclerosis, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, psoriasis, eczema, urticaria, type I diabetes, asthma, conjunctivitis, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, Behcet's syndrome, gout, cancer, viral infections, bacterial infections, organ transplant conditions or skin transplant conditions.

161. The method of Claim 160 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.
162. A method of treating cancer in a subject, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of Claim 136.
163. The method of Claim 162, wherein R^4 is a member selected from the group consisting of (C_1-C_{20}) alkyl, heteroaryl, aryl, heteroaryl (C_1-C_6) alkyl and aryl (C_1-C_6) alkyl.
164. The method of Claim 162, wherein R^4 is benzyl.
165. The method of Claim 162, wherein R^3 is a member selected from the group consisting of (C_1-C_8) alkoxy, (C_3-C_9) heterocyclyl and heteroaryl.
166. The method of Claim 162, wherein R^3 is heteroaryl.
167. The method of Claim 162, wherein R^3 is heteroaryl and R^4 is substituted or unsubstituted benzyl, wherein said substituents are selected from the group consisting of halogen, halo (C_1-C_4) alkyl, halo (C_1-C_4) alkoxy, cyano, nitro and phenyl.
168. The method of Claim 162, wherein R^3 is selected from the group consisting of substituted or unsubstituted pyridyl and substituted or unsubstituted imidazolyl.
169. The method of Claim 162, wherein said compound is administered orally, parenterally or topically.
170. The method of Claim 162, wherein said compound modulates CXCR3.
171. The method of Claim 162, wherein said compound is administered in combination with a second therapeutic agent, wherein said second therapeutic agent is useful for treating cancer.
172. The method of Claim 171 wherein said second therapeutic agent is an antimetabolite or a cytotoxic cancer chemotherapeutic agent.
173. A method of treating cancer in a subject, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound having the formula:



or a pharmaceutically acceptable salt or prodrug thereof wherein:

R^4 is N;

X is -C(O)-;

R^1 and R^2 are members independently selected from the group consisting of H, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, aryl and heteroaryl, or optionally are combined to form a 3- to 8-membered ring having from 0 to 2 heteroatoms as ring vertices;

R^3 is a member selected from the group consisting of (C₁-C₈)alkoxy, amino, (C₁-C₈)alkylamino, di(C₁-C₈)alkylamino and N-(C₃-C₉)heterocyclyl;

R^4 is a member selected from the group consisting of (C₁-C₂₀)alkyl, aryl, aryl(C₁-C₆)alkyl, heteroaryl, heteroaryl(C₁-C₆)alkyl, (C₂-C₂₀)heteroalkyl, aryl(C₂-C₆)heteroalkyl, (C₁-C₆)alkoxy, aryloxy, aryl(C₁-C₆)alkoxy, heteroaryloxy, heteroaryl(C₁-C₆)alkoxy, (C₁-C₆)alkylamino, arylamino, aryl(C₁-C₆)alkylamino, heteroarylamino and heteroaryl(C₁-C₆)alkylamino;

R^{14} is a member selected from the group consisting of (C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, heteroaryl and heteroaryl(C₁-C₈)alkyl;

Q is -C(O)-;

L is (C₁-C₈)alkylene;

the subscript n is an integer from 0 to 4; and

each R_n is independently selected from the group consisting of -R', alkoxy, halogen, perfluoro(C₁-C₄)alkyl, -NO₂, -NR'R'', -S(O)₂R', -S(O)₂NR'R'', -SR', -CO₂R', -CONR'R'' and -NR''C(O)R', wherein R' and R'' are independently selected from the group consisting of H, (C₁-C₈)alkyl, aryl and heteroaryl.

174. The method of Claim 173, wherein R^1 is selected from the group consisting of H and (C₁-C₄)alkyl and R^2 is H.
175. The method of Claim 173, wherein R^3 is a member selected from the group consisting of amino, (C₁-C₈)alkylamino, di(C₁-C₈)alkylamino and (C₃-C₉)heterocyclyl.
176. The method of Claim 173, wherein R^3 is a member selected from the group consisting of amino, propylamino and azetidiny.

177. The method of Claim 173, wherein R^4 is selected from the group consisting of (C_1-C_{20}) alkyl, phenyl, naphthyl, phenyl substituted with halogen, (C_1-C_8) alkyl, (C_1-C_8) alkoxy, nitro, CO_2H , methylenedioxy, trifluoromethyl, phenyl or vinyl, heteroaryl, heteroaryl substituted with (C_1-C_6) alkyl and benzyloxymethyl.
178. The method of Claim 173, wherein R^4 is a member selected from the group consisting of (C_1-C_6) alkylamino, cyclohexylamino and substituted and unsubstituted phenylamino, wherein said substituents are selected from the group consisting of halogen, (C_1-C_8) alkyl, (C_1-C_8) alkoxy and (C_1-C_8) alkylthio.
179. The method of Claim 173, wherein R^4 is selected from the group consisting of substituted phenyl and naphthyl.
180. The method of Claim 173, wherein R^{14} is selected from the group consisting of (C_1-C_8) alkyl, benzyl, phenyl and naphthyl.
181. The method of Claim 173, wherein R^{14} is selected from the group consisting of (C_1-C_8) alkyl, benzyl and substituted phenyl.
182. The method of Claim 173, wherein R^{14} is benzyl or halobenzyl.
183. The method of Claim 173, wherein L is (C_1-C_4) alkylene.
184. The method of Claim 173, wherein each R_a is independently selected from the group consisting of hydrogen, halogen, methyl and trifluoromethyl.
185. The method of Claim 173, wherein
 R^1 is selected from the group consisting of H and (C_1-C_4) alkyl;
 R^2 is H;
 R^3 is a member selected from the group consisting of amino, (C_1-C_8) alkylamino, di (C_1-C_8) alkylamino and (C_3-C_9) heterocyclyl;
 R^4 is selected from the group consisting of substituted phenyl and naphthyl;
 R^{14} is selected from the group consisting of (C_1-C_8) alkyl, benzyl and substituted phenyl; and
each R_a is independently selected from the group consisting of hydrogen, halogen, methyl and trifluoromethyl.
186. The method of Claim 173, wherein
 R^1 is selected from the group consisting of ethyl and propyl;

R² is H;

R³ is a member selected from the group consisting of hydroxy, amino, propylamino and azetidiny;

R⁴ is substituted phenyl;

L is (C₁-C₄)alkylene;

R¹⁴ is benzyl or halobenzyl; and

each R_a is independently selected from the group consisting of hydrogen and halogen.

187. A method of treating a CXCR3-mediated condition or disease in a subject, said method comprising administering to a subject in need of such treatment a therapeutically effective amount of the compound of Claim 136.
188. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is selected from the group consisting of neurodegenerative diseases, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, atherosclerosis, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, psoriasis, eczema, urticaria, type I diabetes, asthma, conjunctivitis, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, Behcet's syndrome, gout, cancer, viral infections, bacterial infections, organ transplant conditions and skin transplant conditions.
189. The method of Claim 188 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.
190. The method of Claim 187, wherein said compound modulates CXCR3.
191. The method of Claim 187, wherein said compound is administered in combination with a second therapeutic agent, wherein said second therapeutic agent is useful for treating neurodegenerative diseases, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, atherosclerosis, encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, psoriasis, eczema, urticaria, type I diabetes, asthma, conjunctivitis, otitis, allergic rhinitis, chronic obstructive pulmonary disease, sinusitis, dermatitis, inflammatory bowel disease, Behcet's syndrome, gout, cancer, viral infections, bacterial infections, organ transplant conditions or skin transplant conditions.
192. The method of Claim 191 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.
193. The method of Claim 187, wherein said organ transplant condition is a bone marrow transplant condition or a solid organ transplant condition.

194. The method of Claim 193, wherein said solid organ transplant condition is a kidney transplant condition, a liver transplant condition, a lung transplant condition, a heart transplant condition or a pancreas transplant condition.
195. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is psoriasis.
196. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is inflammatory bowel disease.
197. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and organ transplant conditions.
198. A method in accordance with Claim 187, wherein said compound is used in conjunction with another therapeutic agent selected from the group consisting of Remicade®, Enbrel®, a COX-2 inhibitor, a glucocorticoid, an immunosuppressant, methotrexate, prednisolone, azathioprine, cyclophosphamide, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, cyclosporine A, D-penicillamine, a gold compound, an antilymphocyte or antithymocyte globulin, betaseron, avonex and copaxone.
199. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is an organ transplant condition and said compound is used alone or in combination with a second therapeutic agent selected from the group consisting of cyclosporine A, FK-506, rapamycin, mycophenolate, prednisolone, azathioprine, cyclophosphamide and an antilymphocyte globulin.
200. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is rheumatoid arthritis and said compound is used alone or in combination with a second therapeutic agent selected from the group consisting of methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine A, D-penicillamine, Remicade®, Enbrel®, auranofin and aurothioglucose.
201. A method in accordance with Claim 187, wherein said CXCR3-mediated condition is multiple sclerosis and said compound is used alone or in combination with a second therapeutic agent selected from the group consisting of betaseron, avonex, azathioprine, copaxone, prednisolone and cyclophosphamide.
202. A method in accordance with Claim 187, wherein said subject is a human.
203. A method for the modulation of CXCR3 function in a cell, comprising contacting said cell with a compound of Claim 136.
204. A method for the modulation of CXCR3 function, comprising contacting a CXCR3 protein with a compound of Claim 136.